Developments in Preclinical Tools to Predict IVIVC

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January 26, 2016
Absorption 101

Factors

Determinants

Formulated Drug → Solubilized Drug → Drug in Enterocyte

Dissolution

Absorption

Solubility

Release Rate

Solubility

Permeability
Limits to Oral Drug Absorption

- Gastric Dissolution
- Aqueous Solubility
- Intestinal Permeability

- Gastric emptying
- Luminal contents
- pH range
- GI transit time
Absorptive Flux

Absorptive Flux (J) = \( C_{int} \cdot P_{wall} \)

\( P_{wall} \) = effective or BCS permeability

\( C_{int} \) = concentration in lumen

IDAS1 Applications

- Fed vs fasted
- Product development
- Comparison of formulations to be manufactured/tested *in vivo*
- Equivalence
BCS Classification

- Class II
- Class I
- Class IV
- Class III

Solubility: Low → High
Permeability: Low → High
Dissolution-Permeability Relationship: Class I

[Graph showing dissolution and permeability over time for Class I propranolol]
Dissolution-Permeability Relationship: Class II

CLASS II
PIROXICAM

DISSOLUTION

% DISSOLVED

TIME (MINUTES)

PERMEABILITY

% PERMEATED

TIME (MINUTES)
Dissolution-Permeability Relationship: Class III
Dissolution-Permeability Relationship: Class IV

CLASS IV
SAQUINAVIR

DISSOLUTION

PERMEABILITY

% DISSOLVED

% PERMEATED

TIME (MINUTES)

TIME (MINUTES)
IDAS2 Applications

- Fed vs fasted
- Product development
- Comparison of formulations to be manufactured/tested *in vivo*
- Equivalence
- Screening solid dosage forms for *in vivo* testing
- Comparison with innovator product
Dissolution-Permeability Data

Dissolution

- % of Dose vs Time (min)
- Green line: Propanolol
- Gray line: Warfarin

Permeability

- % of Dose vs Time (min)
- Green line: Propanolol
- Gray line: Warfarin
Benefits of Caco-2

Caco-2 cells express the most common intestinal efflux and uptake transporters
Correlation: Caco-2 $P_{app}$ vs. Human $F_{abs}$

Minoxidil: $P_{app} \sim 3$
Labetalol: $P_{app} \sim 13$
Pindolol: $P_{app} \sim 17$
Metoprolol: $P_{app} \sim 28$
Antipyrine: $P_{app} \sim 63$

Caco-2 $P_{app}$ $(x10^{-6}$ cm/s), log scale

Oral Bioavailability
Fraction Absorbed
Permeability Internal Standard
Extension of Biowaivers to BCS Class III

- Extension to BCS III
  - High solubility, low permeability
  - Very rapid dissolution (> 85% in 15 min)
  - Qualitatively the same and quantitatively very similar (SUPAC level 1 or 2)
Rat In Situ Intestinal Perfusion
Active Uptake

<table>
<thead>
<tr>
<th>Compound</th>
<th>P_{eff} (x 10^{-4} cm/s)</th>
<th>F_{abs}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>Antipyrine</td>
<td>1.3</td>
<td>100%</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>0.35</td>
<td>100%</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>0.27</td>
<td>90%</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>0.15</td>
<td>90%</td>
</tr>
<tr>
<td>Atenolol</td>
<td>-0.44</td>
<td>50%</td>
</tr>
</tbody>
</table>
Excised Tissue Permeability

- Stomach
- Duodenum
- Jejunum
- Ileum

Pgp
CYP3A4
Esterases
Proteases
Regional Differences
Known tight junction modifiers EGTA and C10 resulted in an increase in test compound and atenolol paracellular permeability.

EGTA and C10 did not affect antipyrine as it exhibits transcellular permeation.
Variability – Representative Tools

<table>
<thead>
<tr>
<th></th>
<th>Excised Tissue</th>
<th></th>
<th>Perfusion</th>
<th></th>
<th>Caco-2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>STD</td>
<td>CV</td>
<td>Mean</td>
<td>STD</td>
<td>CV</td>
</tr>
<tr>
<td>Atenolol</td>
<td>1.65E-6</td>
<td>1.04E-6</td>
<td>57%</td>
<td>7.33E-6</td>
<td>5.22E-6</td>
<td>49%</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>5.59E-6</td>
<td>3.96E-6</td>
<td></td>
<td>9.54E-6</td>
<td>4.47E-6</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>3.04E-6</td>
<td>1.11E-6</td>
<td></td>
<td>1.50E-6</td>
<td>7.20E-6</td>
<td></td>
</tr>
</tbody>
</table>
Components of Bioavailability

- Absorption
  - $f_{abs}$
  - Permeability
  - Solubility

- First Pass
  - $f_G \cdot f_H$
  - Hepatic
  - Intestinal

- Metabolism
Issue-Based ADME: Ported Models

Determine the barriers to bioavailability using surgically modified rats or dogs.

- Chemical Stability
- Solubility
- Dissolution
- Permeability
- Metabolism
- Transporters
  - Protein Binding
  - Biliary Excretion
  - Metabolism: CYPs, UGTs
  - P-gp, MRP2, BCRP

Diagram showing the pathways involved in ADME: Portal Vein, Systemic, Oral, Duodenum, Bile Duct, Colon.
Barriers to Bioavailability - Rat

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Sampling Site</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>JVC</td>
<td></td>
</tr>
<tr>
<td>IPV</td>
<td>JVC</td>
<td>$f_H$</td>
</tr>
<tr>
<td>PO or ID</td>
<td>JVC</td>
<td>$f_{abs} \cdot f_G \cdot f_H$</td>
</tr>
<tr>
<td>IPV vs PO</td>
<td>JVC</td>
<td>$f_{abs} \cdot f_G$</td>
</tr>
</tbody>
</table>
## Barriers to Bioavailability - Dog

### Dose-normalized AUCs for different dosing and sampling regimens

<table>
<thead>
<tr>
<th>Dosing/Sampling Site</th>
<th>DNAUC (hr<em>kg</em>ng/mL/mg)</th>
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</thead>
<tbody>
<tr>
<td>IV/Cephalic</td>
<td>1258</td>
</tr>
<tr>
<td>IPV/Cephalic</td>
<td>959</td>
</tr>
<tr>
<td>ID/Cephalic</td>
<td>933</td>
</tr>
<tr>
<td>ID/PV</td>
<td>1761</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Sampling Site</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID vs IV</td>
<td>CV</td>
<td>$f_{abs} \cdot f_G \cdot f_H$</td>
</tr>
<tr>
<td>ID vs IPV</td>
<td>CV</td>
<td>$f_{abs} \cdot f_G$</td>
</tr>
<tr>
<td>IPV vs IV</td>
<td>CV</td>
<td>$f_H$ (Method 1)</td>
</tr>
<tr>
<td>ID</td>
<td>PV vs CV</td>
<td>$f_H$ (Method 2)</td>
</tr>
</tbody>
</table>
Barriers to Bioavailability - Dog

Method 1: IPV dose + CV sampling vs. IV dose + CV sampling
Barriers to Bioavailability - Dog

Method 1:
IPV dose vs IV dose with CV sampling

Method 2:
ID dose with CV sampling vs. PV sampling
Multi-Platform Approach

Caco-2 Cell Monolayers

Excised Tissue Permeability

Intestinal Perfusion

Ported Animal Models
Building Weight of Evidence

- Product Performance Testing
- IV-IVC
Thank you!

For more information, please email us: contact@absorption.com